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Limb Defects in Homozygous α-Thalassemia: Report of Three Cases

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Homozygosity for the South-Asian α-thalassemia (--^{SEA}/) deletion is a serious hematological condition that results, in most cases, in intrauterine or postnatal death due to anemia and severe hypoxia of prenatal onset. A relationship between congenital abnormalities and intra-uterine hypoxia has been postulated. However, since homozygosity for the (--^{SEA}/) deletion is most common in underdeveloped countries where detailed autopsies are lacking, the incidence of congenital abnormalities among these babies has not been well delineated. We report on three newborn infants, homozygous for the (--^{SEA}/) deletion, who were born with limb defects. We postulate that this combination is the result of prenatal hypoxia which may affect other fetal body organs. This should be taken into consideration when prenatal treatment of affected fetuses, with intrauterine blood transfusion, is suggested. Am. J. Med. Genet. 68:162–167, 1997

KEY WORDS: limb defect; fetal hypoxemia; CVS; α-thalassemia; (--^{SEA}) deletion

INTRODUCTION

The α-globin gene cluster is located at the tip of 16p [Lauer et al., 1980]. Alpha-thalassemia is a genetic condition caused by diminished or absent α-globin chain synthesis. Alpha-thalassemia homozygous (hemoglobin Bart disease) is due to deletion of all four α-globin genes and presents in most cases with hydrops fetalis, hepatosplenomegaly, cardiomegaly, dilation of the intrahepatic umbilical vein, excessive extramedullary hematopoiesis, a large edematous placenta, and various maternal complications [Nakayama et al., 1986; Kazazian, 1990].

Until recently, the condition was regarded as lethal. However, a few cases with hemoglobin Bart disease were born alive [Beaudry et al., 1986; Bianchi et al., 1986; Lam et al., 1992], which suggested that intrauterine blood transfusion might improve their prognosis and avoid intrauterine death. With the experience gained by the prenatal diagnosis and treatment of fetal anemia due to red blood cell isoimmunization, infection with parvovirus B19, and fetal alloimmune thrombocytopenia, intrauterine treatment of fetuses homozygous for α-thalassemia was tried and was successful [Carr et al., 1995]. Such treatments raise many questions regarding the cost, morbidity, and mortality associated with postnatal recurrent transfusions, and eventually bone marrow transplantation [Olivieri et al., 1994].

We report on three fetuses, homozygous for the Southeast-Asian α-thalassemia-1 deletion (--^{SEA}/) with limb defects. The finding that homozygous α-thalassemia may be associated with malformations/disruptions [Liang et al., 1985; Carr et al., 1995] adds another dimension to the clinical spectrum of this condition. Limb abnormalities should be looked for in prenatal ultrasound (U/S) of fetuses affected with α-thalassemia and a discussion of possible limb and perhaps other defects should be included in the genetic

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counselling when the option of intrauterine blood transfusion is raised.

CLINICAL REPORTS

Case 1

The parents were non-consanguineous, of Filipino origin, and this was their third pregnancy. Their first pregnancy resulted in a son who is alive and well. Their second pregnancy was complicated with fetal U/S findings of hydrops fetalis detected at 38 weeks of gestation. Delivery was by Cesarean section and the male infant died shortly after delivery. Autopsy showed extensive extramedullary hematopoiesis. DNA analysis showed that both parents were heterozygous for the Southeast-Asian α-thalassemia-1 deletion ($--^{SEA}/$). In the couple's third pregnancy, amniocentesis was done at 14 weeks of gestation and showed that the fetus was homozygous for ($--^{SEA}/$). The pregnancy was terminated at 16 weeks gestation and autopsy showed transverse defects of upper and lower limbs. There was absence of the 2nd–4th digits on the right hand and on the left hand, the 4th digit and the middle and distal phalanges of the 5th finger were absent. There was absence of the distal part of the right foot and hypoplasia of the distal phalanges of toes 1–5 on the left. The fetus was not hydropic (Fig. 1).

Case 2

A female infant was born to a 29-year-old primigravid woman and a 31-year-old father of Filipino origin. The parents' α-thalassemia carrier state was not tested. Intrauterine growth retardation was detected at 22 weeks of gestation; mild maternal varicella at 24 weeks of gestation was not associated with fever. At 26 weeks of gestation, decreased fetal movements were noted. Fetal bradycardia was noted at 33 weeks of gestation and resulted in an emergency Cesarean section. The infant died shortly after birth. At autopsy, the infant was of appropriate size for gestational age and non-hydropic. Small pericardial and pleural effusions were present and moderate ascites. The right cardiac chambers were dilated and the lungs hypoplastic. The placenta was thick and weighed twice that expected for the gestational age. Extramedullary hematopoiesis was excessive. There were no findings of varicella infection. There was absence of the 1st–4th toes on the right foot and syndactyly of the 2nd-3rd toes on the left (Fig. 2). The fingers were "spade-like" with hypoplasia

Fig. 1. Case 1. **A:** Absence of the 2nd–4th digits on the right and 1st to the 4th digits and the distal phalanges of the 5th finger on the left hand. **B:** Absence of the distal part of the right foot and hypoplasia of the distal phalanges of the 1st–5th toes on the left.

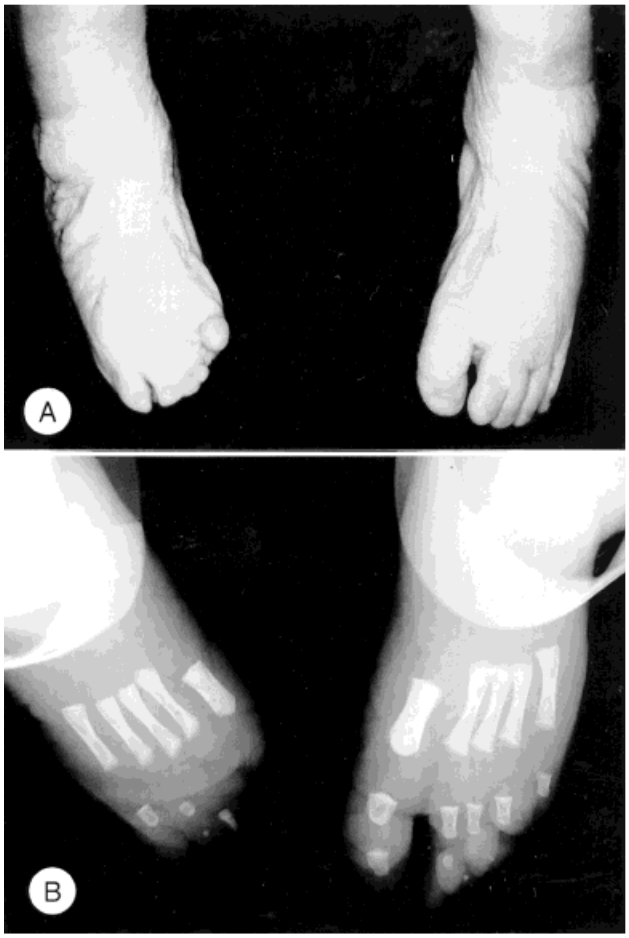

Fig. 2. **A, B:** Case 2. Defects of the 1st–4th toes on the right foot and syndactyly of the 2nd–3rd toes on the left foot.

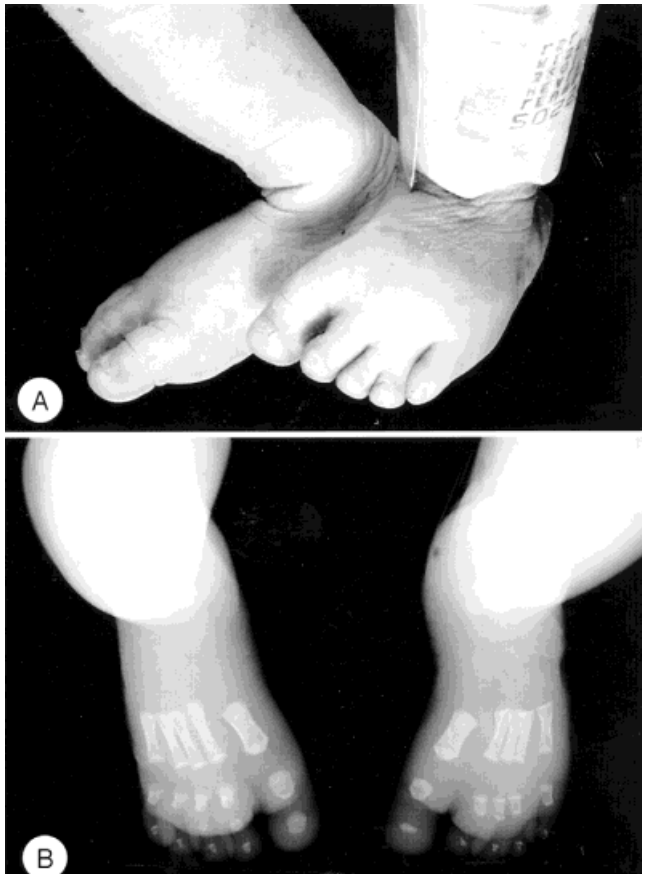

Fig. 3. Case 3. Cutaneous syndactyly of the right 3rd–4th toes (**A**) and radiographs showing absence of the middle phalanges of the right 1st–5th and left 3rd and 4th toes (**B**).

of the distal phalanges. Polymerase chain reaction (PCR) for varicella-zoster virus done on material obtained from multiple fetal organs, including the liver and spleen, was negative. DNA analysis showed that both parents were heterozygous and the infant was homozygous for the (--^{SEA}/) deletion.

Case 3

A male infant was born to a 27-year-old primigravid woman of Chinese descent. The parents' α-thalassemia carrier state was not tested. The pregnancy was complicated with gestational diabetes at 23 weeks of gestation and a urinary tract infection treated with antibiotics one month prior to delivery. Fetal U/S at 18 weeks of gestation was interpreted as normal. A repeat U/S done at 37 weeks of gestation showed cardiomegaly, hepatosplenomegaly, and mild ascites. Delivery was induced and the infant died shortly after birth. Autopsy showed cardiomegaly, hepatosplenomegaly with marked extramedullary erythropoiesis, and mild pulmonary hypoplasia. Cutaneous syndactyly of the 3rd–4th toes on the right was present and roentgenograms showed absence of the middle phalanges of the 1st–5th on the right and the 3rd and 4th toes on the left (Fig. 3). Both parents were heterozygous and the infant was homozygous for the (--^{SEA}/) deletion.

DISCUSSION

The incidence of limb defects (LD) is estimated as 0.6/1,000 livebirths [Kallein et al., 1984; Froster-Iskenius and Baird, 1989]. Terminal transverse limb defects are less common with a frequency of 0.15/1,000 [Holmes, 1992]. LDs are heterogenous and may be the result of a primary abnormality of limb embryogenesis (malformation) or due to an exogenous cause (disruption). Some of the cases which belong to the primary group were reported as being due to a single gene disorder and both autosomal and X-linked LDs have been reported [Zimmer et al., 1985; Al-Awadi et al., 1985; Wulfsberg et al., 1993]. Prenatal exposure to thalidomide, ergot and ergotamine, vitamin A congeners [Rosa et al., 1986; Raymond, 1995; Stephens, 1988], and varicella-zoster (V-Z) may cause LDs. The LD due to V-Z virus infection most probably is the result of neurological insult [Pastuszak et al., 1994]. The mother of case 2 had a varicella infection. However, all cases of LD associated with V-Z infection occurred prior to 20 weeks of gestation while in our case it occurred at 24 weeks of gestation. Moreover, no evidence for fetal infection with V-Z virus was found by PCR.

A group of LDs postulated to be due to abnormal blood supply [Van Allen, 1981, 1992] includes single gene disorders associated with abnormal angiogenesis, such as the Adams-Oliver syndrome [Chitayat et al., 1992], and multifactorial or non-inherited/acquired disorders. The latter includes cases with LD due to amniotic bands, which can cause external compression of blood vessels from entanglement [Higginbottom et al., 1979] or strangulation of a limb by the umbilical cord, constraint from an ectopic pregnancy, a bicornuate uterus, uterine fibroma [Graham et al., 1980], and oligohydramnios [Houben, 1984]. Occlusion of blood vessels by emboli and thrombosis can occur in maternal diabetes mellitus [Van Allen et al., 1989] or prenatal exposure to cocaine [Hoyme et al., 1990], misoprostol [Gonzalez et al., 1993] and ergot [Hughes et al., 1988].

Recent publications have suggested that infants born to mothers who had chorionic villus sampling (CVS) in the first trimester of pregnancy have an increased incidence of LD and the hypoglossia-hypodactyly (Hanhart) anomaly [Burton et al., 1992]. In most of these, CVS had been done before 9 weeks of gestation. Direct hysteroscopic observations in human pregnancies terminated immediately after transabdominal single-needle aspiration support the view that the pathogenesis in these cases is placental trauma, leading to apparent hypoperfusion and peripheral hypoxia or embolization of fetal vessels by placental fragments broken during CVS [Scott, 1991; Rodeck, 1993]. Such emboli can lead to distal limb necrosis and developmental arrest and thus a LD [Rodeck, 1993].

Occlusion of blood vessels with resulting LD can also be caused by inherited hematological conditions. Petter et al. [1977] reported on an animal model, the brachydactyly (br) rabbit, whereby rabbits homozygous for the brachydactyly mutation (br/br) developed fetal polycythemia and macrocytosis. This caused occlusion of blood vessels in the digits and thus brachydactyly.

Perhaps the best human model to study the effect of prolonged hypoxia on the developing fetus is the fetal α-thalassemia-homozygous state. This cluster includes the genes for ζ2, ζ1, pseudo α1, and 2 α-globin genes: α1 and α2. The normal hemoglobin tetramere consists of a pair of α-like chains interlocked with a pair of β-like chains. Initially, the hemoglobin synthesis is restricted to the yolk sac. At 3–6 weeks post-conception, 2 α-like ζ chains unite with 2 β-like ϵ chains to form the first embryonic hemoglobin: Gower 1. Studies showed that embryonic red blood cells carry the same oxygen dissociation curve as human fetal red cells [Huehns and Farooqui, 1975]. Other hemoglobins formed during embryogenesis are the Gower 2 (α2ϵ2) and hemoglobin Portland 1 (ζ2γ2). Production of the ζ and ϵ globin chains ceases by the 10th week post-conception and is superseded by the synthesis of γ chains. At about 6 weeks post-conception, the fetal liver takes over and synthesizes predominantly α an γ globin chains which combine to form fetal hemoglobin, the predominant hemoglobin of fetal life, which persists as a minor component throughout adulthood [Weatherall, 1995]. Deletion of all four α-globin genes results in α-thalassemia-1 homozygous or hemoglobin Bart disease. Since no α-globin chains can be synthesized in this condition, the predominant hemoglobin is hemoglobin Bart (γ4), with 5–20% hemoglobin Portland 1 and traces of hemoglobin H (β4). Hemoglobin Bart has an extremely high oxygen affinity, so that hardly any or no oxygen is transported to the tissues. Typically, fetuses homozygous for the α-thalassemia-1 deletion present in the second and third trimester with ascites, hepatomegaly, cardiomegaly, oligohydramnios, and thick placenta [Chan et al., 1984; Ghosh et al., 1987; Kanokpongsakdi et al., 1990] and only at a later stage develop hydrops fetalis. The hydrops is most probably the result of congestive heart failure and hypoalbuminemia [Ghosh et al., 1987]. Another possible contribution to the acral hypoxemia in these fetuses is obstruction of the small blood vessels. Butthep et al. [1992] reported that red blood cells from patients with hemoglobin H disease bind to endothelial cells at a greater number than in control fetuses and Bunyaratvej et al. [1992] showed that thalassemic serum impairs the growth of the endothelial cells in vitro. Moreover, Laosombat et al. [1992] found spontaneous platelet aggregation in thalassemic children and adults. If such a mechanism exists in fetuses with homozygous α-thalassemia it could cause occlusion and impaired growth of blood vessels with subsequent disruption of end organs of affected vessels.

α^0 Thalassemia is a common condition in Southeast Asia with the carrier incidence of $(--^{SEA}/\ )$ type of a thalassemia deletion being as high as 15% in countries such as China, Thailand, Vietnam, and the Philippines [Weatherall, 1995]. Since the condition is usually lethal and most cases are born in developing countries, detailed findings on fetal autopsies are often lacking. In 1985, Liang et al. published their experience with 46 pregnancies with affected fetuses. Premature delivery occurred in 93% of the cases at a mean gestational age of 32.2 weeks and 17.4% of the infants presented with malformations such as digit malformation, hydrocephaly and microcephaly. A detailed description of the abnormalities was not given. Furthermore, in a review of the manifestations associated with homozygous α-thalassemia, Fuchareon and Winiichagoon [1992] concluded that fetuses affected with this condition have abnormal development of organs such as brain and lungs.

In 1994, we reported on two cases with homozygous α-thalassemia and LD [Chitayat et al., 1994]; here we add a third case with this combination. Following our initial report, two more articles supporting this hypothesis were published. Harmon et al. [1995] reported on a fetus of Thai descent, who presented at 20 weeks of gestation with symmetrical terminal transverse limb defects. On autopsy, the fetus was found to have extramedullary hematopoiesis suggesting thalassemia and the parental blood films were consistent with heterozygosity for thalassemia. However, the parental and fetal hematological condition was not delineated. Dissection of the limb stumps demonstrated strips of calcified acellular material running parallel to the skin surface beneath the epidermal surface of the nubbins and resembled infarcted blood vessels. The second case reported by Carr et al. [1995] was a fetus with homozy-

gous α-thalassemia, upper and lower limb abnormalities, and hypospadias [the same case was also reported by Abuelo et al., 1994]. This infant was treated successfully with intrauterine transfusion, was born alive with multiple abnormalities, and currently needs recurrent transfusions. However, not all patients with this condition who were born alive had intrauterine blood transfusion [Beaudry et al., 1986; Bianchi et al., 1986; Lam et al., 1992]. Although the most plausible explanation for the association of limb defect with homozygous α-thalassemia is vascular disruption, it is also possible that the α-globin genes, which are deleted in patients with the ($--^{SEA}$/) deletion and/or other genes located nearby, have a major role in limb embryogenesis.

The improvement of the intrauterine transfusion technique, and the substantially decreased risk for miscarriage and prematurity associated with this procedure, provides a tool to treat patients homozygous for α-thalassemia to prevent their intrauterine death and the maternal complications associated with this condition [Carr et al., 1995]. However, the use of this procedure in affected fetuses has raised ethical questions regarding long-term prognosis of such babies who will need a lifetime of transfusions, not to mention the morbidity and mortality associated with hemosiderosis, hepatitis, and HIV infection and, ultimately, the need for bone marrow transplantation, which is a costly procedure with high mortality and morbidity [Olivieri et al., 1994]. The finding that fetuses homozygous for α-thalassemia-1 deletion may also have associated abnormalities such as limb defects provides a new facet of this condition that is of importance as it influences the decision-making process to treat these patients. Thus, if the medical and ethics team reaches a decision to provide the parents with the option of intrauterine transfusion which will result in the birth of a liveborn child with this condition, every attempt should be made to detect fetal malformations by detailed U/S. The parents should be informed of the possibility that some fetal malformations associated with this condition may not be diagnosed by fetal U/S as well as the prenatal and lifelong postnatal complications associated with repeated blood transfusions and bone marrow transplantation. In the future, gene therapy will reduce the side effects associated with repeat blood transfusions and allogenic bone marrow transplantation. However, it may not avoid the limb defects and other fetal abnormalities associated with hemoglobin Bart's disease if these are the result of intrauterine hypoxia or gene/genes deleted in cases with the ($--^{SEA}$) mutation.

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